DETAILED ACTION

Claims 1-24 are pending and are subject of this office action.

Claims 17-20 are withdrawn as being drawn to a non-elected invention.

Claims 1-16 and 21-24 are currently under consideration.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 05/19/2006. The Examiner has considered the reference cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Election/Restrictions

Applicant's election of invention 1 (claims 1-16 and 21-24) without traverse in the reply filed on 09/09/2008 is acknowledged.

Claims 17-20 are withdrawn from consideration and claims 1-16 and 21-24 will be examined in the instant office action.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-8, 11, 13-16 and 21-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Linder et al (US 2003/0003058) as evidenced by the European Pharmacopeia (pages 282-283)

Linder discloses lyophilized pantoprazole preparations which are obtainable by freeze-drying of aqueous solutions of pantoprazole (abstract). Linder discloses that injectable solutions, including solutions constituted from sterile solids intended for parenteral use should be free essentially free form particles that can be observed on visual inspection and for patient safety it is also desirable to have a low number of subvisible particles [0007]. Linder discloses that by freeze drying of an aqueous solution of pantoprazole, ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate a lyophilisate is obtained having significantly lower number of subvisible particles after reconstitution with a solvent [0007]. Linder discloses that pantoprazole and/or a salt may contain various amounts of solvents which isolated in crystalline form and discloses that the pantoprazole in his invention refers to pantoprazole sodium sesquihydrate ([0008] and claim 4). Pantoprazole Injection according to Linder's invention can be produced by dissolving the lyophilized product thus obtained in a suitable solvent and preferably the pantoprazole injection according to the invention is used in the form of intravenous injection [0010]. The lyophilized product and pantoprazole injection according to the invention preferably contain pantoprazole in the dose customary for the treatment of the respective disease. The administration of the daily dose (e.g. can be carried out, for example, in the form of an individual dose or by means of a number of doses of the

administration forms according to the invention and for bolus administration 20 to 120 mg of lyophilized product according to the invention can be reconstituted with 10 ml physiological saline [0011]. In example 1 Linder discloses the production of lyophilized pantoprazole under nitrogen atmosphere, wherein the formulated solution is filled into vials which are semi stoppered and put into the freeze-dryer for lyophilization [0014]. Linder describes light obscuration particle test counts for his injection product where in less than 120 particles per vial, the particles having the size equal to or greater as 10 µm ([0019-0021] and claim 13).

As to the use of the instantly claimed butyl rubber stoppers of type 1 kind taught by European pharmacopeia. European pharmacopeia discloses the specifications for use of Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders (section 3.2.9, page 282). European pharmacopeia discloses the types of rubber closures into type I closures which meet the strictest requirements and which are preferred; type II closures which have mechanical properties suitable for special uses, but cannot meet requirements as severe as those of type I (paragraph 1 under section 3.2.9) and further elaborates on the properties of the closures (paragraph 2, under section 3.2.9). Finally, the pharmacopeia discloses the extractable zinc limit to be less than or equal to 5 µg per ml of reconstituted injection solution (page 283, extractable zinc section). Accordingly, European pharmacopeia has set standards for glass vials and rubber closures to be used in the manufacture of injectable. In order to obtain marketing and selling privileges for the pharmaceutical products one has to adhere to the guidelines set by the pharmacopeia. Accordingly,

absence of any evidence to the contrary, the vials and closures used by Linder would be well within the specifications set by the pharmacopeia such that it passes all the recommended tests including the extractable zinc test.

Accordingly claims 1-3, 5-8, 11-16 and 21-24 are anticipated by Linder et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linder et al (US 20030003058) as evidenced by the European pharmacopeia in view of Nakanishi et al (US 5589491) further in view of Muraki (US6645635).

Linder teaches lyophilized pantoprazole preparations which are obtainable by freeze-drying of an aqueous solution of pantoprazole (abstract). Linder teaches that injectable solutions, including solutions constituted from sterile solids intended for parenteral use should be free essentially free form particles that can be observed on visual inspection and for patient safety it is also desirable to have a low number of subvisible particles [0007]. Linder teaches that by freeze drying of an aqueous solution of pantoprazole, ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate a lyophilisate is obtained having significantly lower number of subvisible particles after reconstitution with a solvent [0007]. Linder teaches that pantoprazole and/or a salt may contain various amounts of solvents which isolated in crystalline form and teaches that the pantoprazole in his invention refers to pantoprazole sodium sesquihydrate ([0008] and claim 4). Pantoprazole Injection according to Linder's invention can be produced by dissolving the lyophilized product thus obtained in a suitable solvent and preferably the pantoprazole injection according to the invention is used in the form of intravenous injection [0010]. The lyophilized product and pantoprazole injection according to the

invention preferably contain pantoprazole in the dose customary for the treatment of the respective disease. The administration of the daily dose (e.g. can be carried out, for example, in the form of an individual dose or by means of a number of doses of the administration forms according to the invention and for bolus administration 20 to 120 mg of lyophilized product according to the invention can be reconstituted with 10 ml physiological saline [0011]. In example 1 Linder teaches the production of lyophilized pantoprazole under nitrogen atmosphere, wherein the formulated solution is filled into vials which are semi stoppered and put into the freeze-dryer for lyophilization [0014]. Linder describes light obscuration particle test counts for his injection product where in less than 120 particles per vial, the particles having the size equal to or greater as 10 µm ([0019-0021] and claim 13).

As to the use of the instantly claimed butyl rubber stoppers of type 1 kind taught by European pharmacopeia. European pharmacopeia discloses the specifications for use of Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders (section 3.2.9, page 282). European pharmacopeia discloses the types of rubber closures into type I closures which meet the strictest requirements and which are preferred; type II closures which have mechanical properties suitable for special uses, but cannot meet requirements as severe as those of type I (paragraph 1 under section 3.2.9) and further elaborates on the properties of the closures (paragraph 2, under section 3.2.9). Finally, the pharmacopeia discloses the extractable zinc limit to be less than or equal to 5 µg per ml of reconstituted injection solution (page 283, extractable zinc section). Accordingly, European pharmacopeia has

set standards for glass vials and rubber closures to be used in the manufacture of injectable. In order to obtain marketing and selling privileges for the pharmaceutical products one has to adhere to the guidelines set by the pharmacopeia. Accordingly, absence of any evidence to the contrary, the vials and closures used by Linder would be well within the specifications set by the pharmacopeia such that it passes all the recommended tests including the extractable zinc test.

Linder is silent as to the proton pump inhibitor being omeprezole or esomeprazole instead of pantoprazole in the injection product and the use of butyl rubber stopper of type I, which is partially fluoro-polymer laminated.

However Nakanishi teaches an injection of a benzimidazole compound or a salt thereof, particularly sodium salt of omeprazole causing less side-effects such as hemolysis, and less local irritation, which salt permits easy formulation (col.1, lines 63-67). Nakanishi teaches that, an injection of the benzimidazole compound or salt thereof can be prepared by dissolving the benzimidazole compound or salt thereof in water for injection, etc. along with a strong alkaline compound (col.2, lines 54-59) Nakanishi additionally teaches that this alkaline aqueous solution is lyophilized by a method known per se (col. 3, lines 1-4). Additionally Nakanishi teaches that the injection of his invention can be produced by dissolving the lyophilized product thus obtained in an aqueous solvent (col. 3, lines 10-12) and the can be used, for example, in the form of drip infusion, intravenous injection, intramuscular injection, subcutaneous injection (col. 3, lines 17-19).

Muraki teaches laminated rubber stoppers with an improved thermoplastic film-lamination for the medicament vial (abstract). Muraki teaches that a stopper material of a medicament vessel, is required to have heat resistance, compression strain resistance, enriched softness, chemical inertness and low permeability to gases or water and states that with respect of the sealing property, rubbers (both natural and synthetic such as butyl rubber) are excellent as stoppers. Muraki teaches that problems such as t vulcanizers, compounding agents, etc. contained in the rubbers dissolving in medicaments in the vials, absorption of the medicinal contents on rubber surfaces and contamination due to fine particles leaching from the rubber materials during production steps or storage of medicaments occurs (col. 1, lines 13-28). Muraki teaches a laminated rubber stopper for a medicament vial, in which the whole lower surface or the whole lower surface and a part of the upper surface of the rubber body is laminated with a thermoplastic film (col.2, line 65 to col.3, line 1). Muraki teaches a laminated rubber stopper for a medicament vial, to be a thermoplastic film is a tetrafluoroethylene resin film or a modified tetrafluoroethylene resin (col.3, lines 8-11). In Table 4, compounding example 1, Muraki teaches Butyl Rubber which subsequently laminated with polytetrafluroethylene (PTFE-1) film (col.9, lines 15-67). Finally Murki teaches the advantages of the Present Invention that it provides a rubber stopper for a vial, in which the whole lower surface or the whole lower surface and a part of the upper surface is laminated with a thermoplastic film such as PTFE, etc. to prevent the rubber from elution of medicaments and provide excellent sealing.

The references used supra are silent with reference to the extracted zinc levels at less than or equal to 5 µg or the reduced pressure at which the inside of the vial needs to occur in. With respect to the claimed concentrations of extracted zinc in the rubber stoppers used, European, US or Japanese pharmacopeia sets standards for the extractable zinc content in the rubber stoppers used for vials as evidenced above where in that amount is less than 5 µg/ml solution. Absence of any evidence to contrary, the amount of extractable zinc in the rubber stoppers taught in the prior art would be less than 5 µg/ml so as to meet the set standards. With reference to the pressure requirements, lyophilization process as taught by Linder involves freeze drying under reduced pressure and vacuum which creates an atmosphere of reduced pressure inside the sealed vial. Although the exact pressure is not taught by Linder, one of ordinary skill in the art would be able to optimize the lyophilization parameters to achieve the claimed pressure. It is incumbent upon the applicant to provide evidence or comparative data to the contrary. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In view of the foregoing references, the instantly claimed pharmaceutical product would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Linder and Nakanishi teach freeze-dried injectable formulations of Pantoprazole and osmeprozole respectively in glass vials with rubber stoppers. Muraki teaches rubber stoppers such as butyl stoppers which are laminated with a fluoro-polymer and additionally teaches the advantages of inclusion of the polymer lamination

to the rubber stopper. Accordingly all of the materials instantly claimed were known in the art at the time and would have motivated an ordinarily skilled artisan to produce an injectable formulation of pantoprazole in combination with EDTA within a standardized vial. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that an injectable product thus formulates will have excellent stability, with less leaching and leaking prospects.

Conclusion

Claims 1-16 and 21-24 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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